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Intravascular Lymphomatosis Presenting as Adult Respiratory Distress Syndrome

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An unusual case of intravascular lymphomatosis caused by small noncleaved, non-Burkitt's lymphoma, which presented with adult respiratory distress syndrome, is described. Extensive invasion of the small- and medium-size blood vessels of the lung, liver, spleen, kidneys, heart, esophagus, stomach, small and large intestines, bladder, and brain—but not the bone marrow or peripheral blood—is documented. The possible mechanism and the unusual features of this case are discussed in comparison with previously reported cases. The pertinent literature is reviewed. The problem of diagnosing this pathological entity is emphasized. Am. J. Hematol. 56:155–160, 1997.

Key words: lymphoma; intravascular lymphomatosis; adult respiratory distress syndrome

INTRODUCTION

Intravascular lymphomatosis (IVL) or ''angiotropic lymphoma'' is a rare form of aggressive, disseminated, malignant lymphoma characterized by widespread intravascular proliferation of neoplastic lymphocytes within the lumina of small blood vessels of various organs with little or no involvement of the adjacent parenchyma [1]. The disease was first reported by Pfleger and Tappeiner in 1959 who considered it a malignant endothelial disorder that they called angioendotheliomatosis proliferans systemisata [2]. It was shown to be a malignant lymphoma by Bhawan et al. and by Carrol and associates in 1985 [3,4], and reclassified as IVL by Wick and coworkers [5] and as angiotropic lymphoma by Sheibani et al. in 1986 [6]. In 1988 Ferry et al. demonstrated B-cell markers in IVL [7] and in 1990 Molina and associates showed that lymphoma cells infiltrating lymph nodes were cytologically identical to intravascular malignant cells [8]. The malignant lymphocytes in all cases of IVL studied thus far have been described as large cell lymphoma, including a case of IVL with hepatic, splenic, and cutaneous blood vessel involvement recently published by Carter et al., which possibly evolved from a low-grade, follicular, small cleaved-cell lymphoma [9]. We describe an unusual case of disseminated IVL involving the lung, liver, spleen, kidney, heart, bowels, bladder, and brain, which presented with adult respiratory distress syndrome (ARDS) and was caused by high-grade, small noncleaved cell lymphoma. To our knowledge, this is the first reported case of IVL caused by non-large cell lymphoma and that was clinically masquerading as ARDS.

CASE REPORT

A 67-year-old Caucasian female was found to have a mass in her right breast in April 1992. An excisional biopsy revealed a high-grade, aggressive B-cell lymphoma characterized as a small noncleaved, non-Burkitt's lymphoma. Extensive workup revealed no other areas of tumor involvement. She was treated with local radiation therapy (5,500 cGY) and was followed with semiannual evaluation and annual computerized tomograms of the chest and abdomen and annual mammograms. These studies performed 7 months prior to the onset of her final illness were unremarkable. In May 1996, 4 years after her breast biopsy, she developed an acute febrile upper respiratory illness with otalgia and headaches, which persisted beyond 1 week despite anti-

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biotic treatment. She was hospitalized with a 103° fever and a dry hacking cough; in spite of aggressive medical management including intravenous polyantimicrobial therapy, she developed respiratory failure requiring assisted ventilation.

On admission, fever and bilateral pulmonary rhonchi were the only abnormal findings on examination. She had no lymphadenopathy or hepatosplenomegaly. Her hemoglobin and hematocrit were 11.5 g and 34.3%, white cell count of 5,200 with slight left shift, platelet count of 212,000, and normal chemistries except for moderately elevated LDH and angiotensin converting enzyme (ACE) level of 204 (normal < 55). The peripheral blood smear was unremarkable. Chest X-rays showed bilateral infiltrates that progressed to ARDS within 4 days after admission. Bronchoscopy, bronchial lavage, and transbronchial biopsies were nondiagnostic. A CT scan of the brain was normal. All routine cultures, tests for Legionella, pneumocystis, cytomegalovirus, and coccidiomycosis were negative; cold agglutinin and mycoplasma titers were borderline (1:32 and 1:8, respectively). Antibiotic and antifungal coverage was expanded and intravenous gamma globulin was infused because of low level of IgG (532 mg%). She became hypotensive and unresponsive, developed hepatomegaly, abnormal liver function tests, and thrombocytopenia (platelet count of 65,000) without evidence of disseminated intravascular coagulation (DIC). Recurrent occult lymphoma with lymphangitic spread to the lungs was suspected but repeated bronchoscopy and biopsy were unrevealing. A computerized tomogram of the abdomen showed modest diffuse hepatosplenomegaly but no evidence of lymphadenopathy or retroperitoneal mass lesion. Her LDH rose to 1,702 with an alkaline phosphatase of 342 (normal < 130), and normal beta-2 microglobulin (2.7). She developed lymphopenia (absolute lymphocyte count of 600), depressed CD4 lymphocytes, and a reversed CD4/CD8 ratio. An HIV test was negative. Mild anemia and normal WBC persisted; no abnormal cells were noted in the peripheral blood smear. A bone marrow aspiration and biopsy were nondiagnostic. Liver biopsy and open lung biopsy were scheduled but had to be deferred because of the development of DIC not correctable with fresh frozen plasma. A therapeutic trial with high-dose dexamethasone (20 mg IV q12h for 4 days) was begun resulting in a dramatic but transient improvement. The patient became afebrile, alert, and normotensive; liver function tests and chest films showed marked improvement, but she could not be weaned off the ventilator. Subsequently she developed abdominal distention; steroids were tapered, and she became febrile (102 to 103°). The LDH increased to 1,842, uric acid to 12.3 mg percent with creatinine of 1.3 and she became acidotic (pH 6.8). Her respiratory condition worsened, necessitating an increase in PEEP to 8; she developed anemia (Hb/Hct of 8.4 g/26.1%) requiring transfusion with packed red cells. The abdomen became more distended, the white cell count increased to between 10,000 to 20,000, and she developed progressive lactic acidosis (13.2 to 20.3), with DIC, hypotension, and multi-organ failure. Abdominal sepsis due to ischemic bowel or perforated viscus was suspected but not found on laparoscopic exploration that showed no abscess, lymphoma, or other mass lesion. A ''cirrhotic-looking liver'' was observed but was not biopsied because of the severe coagulopathy. Rapid deterioration continued, and she died of multisystem end-organ failure, ARDS, and lactic acidosis of ''unknown etiology'' on the eighteenth day of hospitalization. An autopsy was subsequently performed.

PATHOLOGY

The breast biopsy of 1992 showed morphologic and immunohistochemical findings indicative of a small noncleaved non-Burkitt's lymphoma.

An autopsy there was no evidence of lymphoma in the breasts; no cutaneous lesions and no lymphadenopathy were noted. The viscera showed pulmonary congestion with multicentric hemorrhages and moderate hepatosplenomegaly. Microscopic examination of the lungs showed the alveolar capillary beds distended by atypical lymphocytes with morphological features identical to those noted in the prior breast biopsy (Fig. 1). Similar intravascular involvement was also noted in the liver, spleen, accessory spleen, kidneys, heart, esophagus, stomach, small and large intestines, bladder, and brain (Figs. 2,3). The bone marrow and the adrenal glands showed no involvement. The lymphoid cells were leukocyte common antigen positive, CD20 positive, CD3 negative, kappa positive, lambda negative, and thus consistent with small noncleaved non-Burkitt's etiology. In addition, the neoplastic cells were EBER negative by in situ hybridization.

DISCUSSION

This 71-year-old woman succumbed to multisystem end-organ failure, lactic acidosis, and ARDS caused by widespread invasive IVL 4 years after treatment for a localized high-grade, noncleaved, non-Burkitt's, small-cell lymphoma of the breast. ARDS was probably caused by the extensive invasion of the pulmonary capillary bed with neoplastic lymphocytes that did not spread into the parenchyma. We suspect that the spleen and the accessory spleen may have served as a reservoir of the lymphoma, which could have disseminated as the patient became immunocompromised by an intercurrent viral illness. In some respects our case is similar to those re-

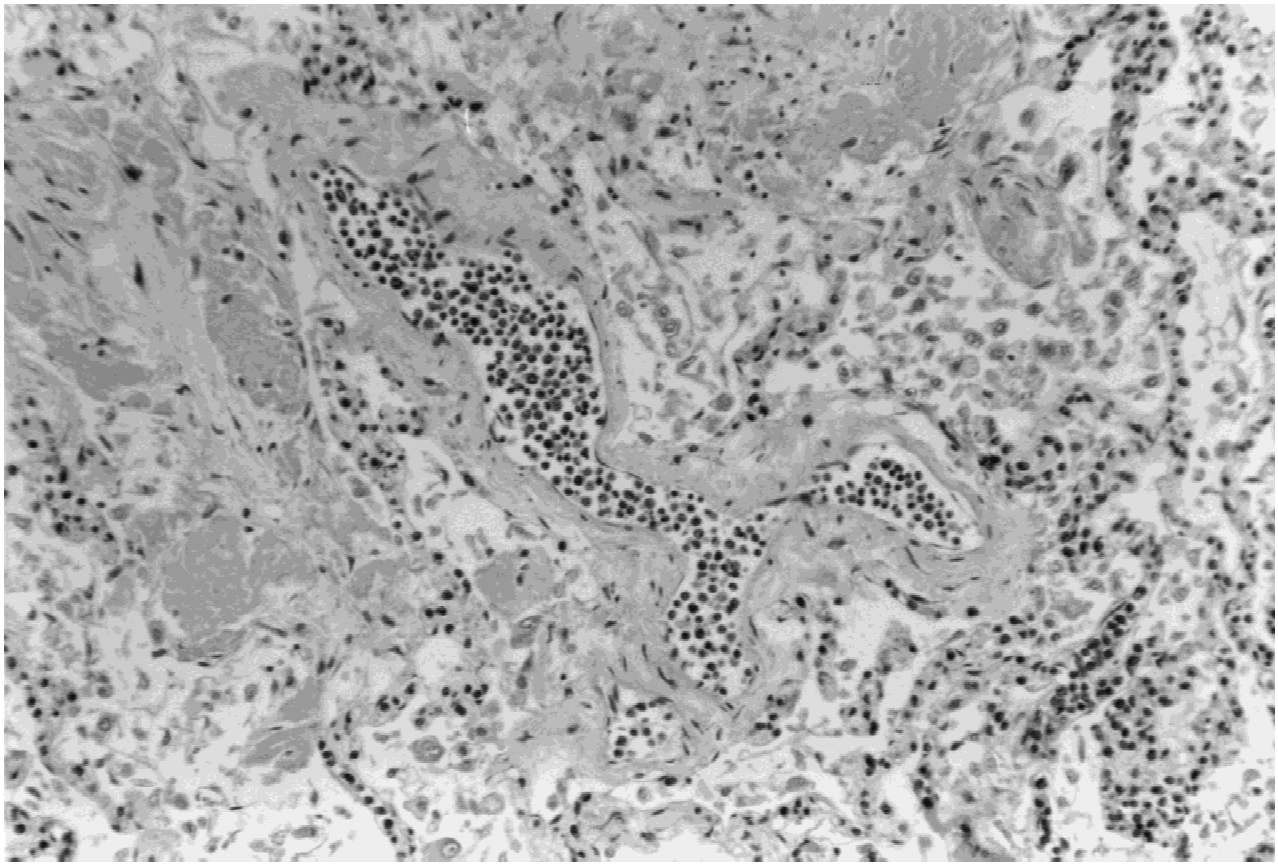

Fig. 1. Prominent vascular involvement of the lung by atypical lymphocytes. Note distention and virtual obstruction of the vascular channels by lymphoma.

ported earlier. A review of the literature reveals that intravascular lymphomatosis is an uncommon aggressive non-Hodgkin's lymphoma, mostly of B-cell lineage [3,5,7,10–12]. It is characterized by multifocal intravascular proliferation of neoplastic lymphocytes, usually without parenchymal or bone marrow invasion [11–15]. The lymphatic system may be involved without enlargement of the lymphnodes [11,12,16–18], which occasionally may show extravascular, parenchymal invasion [5,8,12,17]. A T-cell variant of IVL has also been described [6,9,17,19–21]. Circulating malignant lymphocytes are rarely demonstrable in the peripheral blood despite the large number of intravascular tumor cells distending or obstructing the capillaries and small blood vessels of various organs [11,16–18]. In most cases IVL is a primary neoplastic growth, while others represent dissemination from occult foci of lymphoma [11,18]. The special affinity of IVL cells to intraluminal endothelium is probably related to alterations in lymphocyte surface receptors. The presence of special adhesion molecules or ''homing receptors'' that recognize endothelial cells and facilitate migration into lymph nodes has been demonstrated on normal as well as neoplastic lymphocytes [4,7,22,23]. Gallatin and coworkers postulated the absence of specific homing receptors on neoplastic lymphocytes [24] but Ferry et al. showed that homing receptors per se are not sufficient to facilitate lymphocyte migration [7]. Carrol et al. suggested that neoplastic lymphoid cells are trapped within small vessels due to lack of a surface receptor molecule enabling lymphocyte migration [4]. Jalkanen and associates found that the CD18 surface glycoprotein, which normally facilitates lymphocyte egress from blood vessels, was not expressed or was only weakly expressed on the Hermes-3-antibody defined homing receptors of neoplastic lymphocytes [25].

The most common presenting symptoms in IVL are persistent fever and neurological symptoms such as dementia, and various cutaneous lesions [10,12,18,26–30]. Dyspnea, due to pulmonary capillary obstruction [31], adrenal insufficiency [32], and thrombotic thrombocytopenic purpura [33] were also reported as presenting symptoms. In some cases the diagnosis was made by renal biopsy [12,34,35], or was coincidental to prostatectomy or cholecystectomy [12,36,37]. Demirer et al. described a case of IVL presenting with fever, cough, dyspnea, and hypoxemia, yet with normal chest films, com-

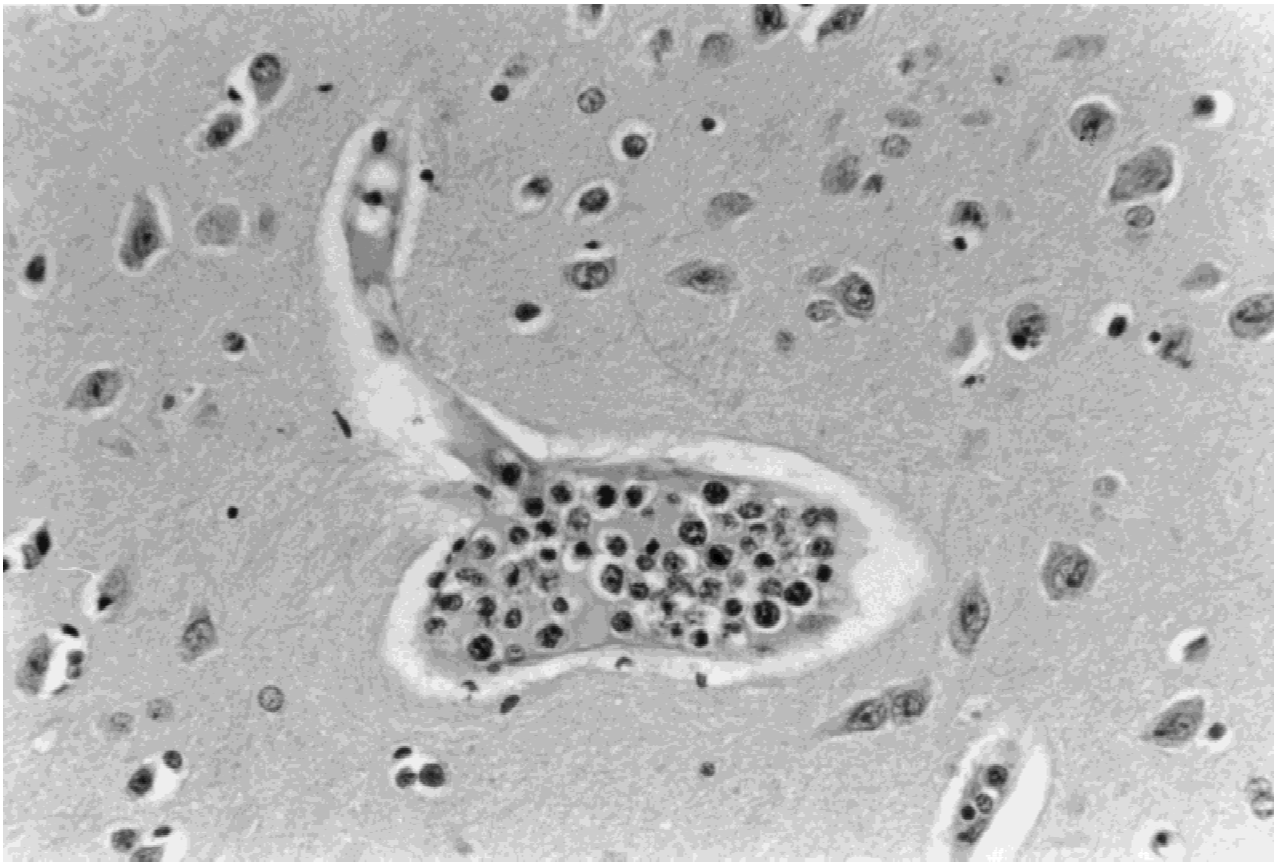

Fig. 2. Intravascular lymphomatosis invading vascular channels of the brain.

puterized tomogram, and pulmonary angiogram [11]. Other cases presenting with respiratory symptoms were also published [5,17,31,38–40]. A significant number of patients had serological evidence of autoimmunity [5,12].

The clinical course of the illness is characterized by widespread and rapidly fatal end-organ failure from the proliferation of neoplastic aggregates within the lumina of small blood vessels in various organs. The median survival was reported to be 5 months [8]. The majority of cases were diagnosed by post-mortem examination [11] although recent reviews suggest that IVL can be diagnosed before death by biopsies of the brain, skin, lung, or kidney [10,12]. Transient good responses to high-dose steroids were described and prolonged survival with durable remission was reported following polychemotherapy [6,11,12,17,41].

In our case the clinical picture was dominated from the onset by fever, respiratory symptoms, and the rapid development of severe ARDS. Typical neurological symptoms or skin lesions were absent. A most extensive search failed to find an underlying etiology for the ARDS, which was evidently caused by occlusive invasion of the pulmonary capillary bed by malignant lymphocytes. The widespread disease was confined to vascular channels, and parenchymal invasion was only seen in the spleen.

The major difference between our case and those published previously is the type of lymphocytes invading the microvasculature. Although possible evolution of large cell IVL from small cell follicular lymphoma was described recently [9], virtually all cases of IVL have been attributable to large cell lymphoma. Our case appears to be the first IVL caused by small noncleaved, non-Burkitt's type high-grade lymphoma, with the clinical presentation of ARDS. An elevated level of ACE was described in only one previous case of IVL [42].

CONCLUSION

The case presented here demonstrates the pitfalls that may be encountered in the diagnosis of IVL given the absence of peripheral blood or bone marrow involvement or lymphadenopathy, and a clinical picture dominated by specific end-organ failure. Clinical attention was focused on a possible infectious etiology for ARDS, which followed a febrile respiratory illness. In spite of strong suspicion of recurrent lymphoma, multiple transbronchial lung biopsies, bone marrow biopsy, and various imaging studies failed to reveal the underlying pathology, and

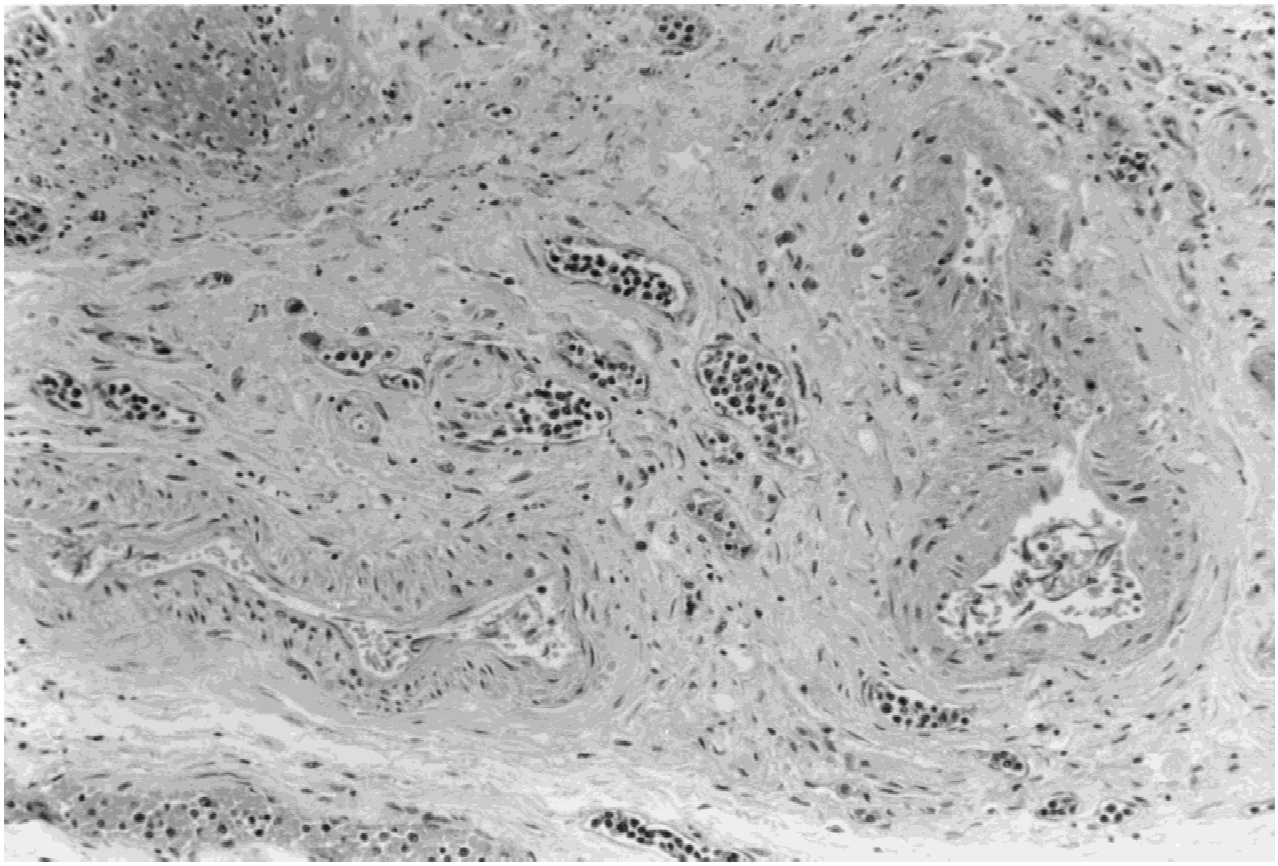

Fig. 3. Intravascular lymphomatosis invading vascular channels of the bladder wall.

serial blood smears did not show abnormal lymphocytes until the terminal phase of the illness.

This case illustrates the need to consider IVL as a possible cause of ARDS particularly in patients with a prior history of lymphoma. It also suggests that IVL is not exclusively caused by large cell (or immunoblastic) lymphoma. Furthermore, this case also demonstrates the continued value of post-mortem examination in the age of sophisticated imaging studies.

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